

REMARKS

Claims 1-29 are pending in the present application.

At the outset, Applicants wish to thank Examiner Weddington for the helpful and courteous discussion with their undersigned Representative on August 15, 2005. During this discussion, various arguments and potential amendments were discussed to address the outstanding rejection. The content of this discussion is believed to be reflected in the present response. Applicants also wish to thank Examiner Weddington for the recognition that Claims 5, 9, 11, and 29 are free of the art and allowable. Reconsideration of the outstanding rejections is requested in view of the following remarks.

The rejection of Claims 1-4, 6-8, 10, and 12-15 under 35 U.S.C. §112, first paragraph (enablement), is respectfully traversed.

It is the Examiner's position that the present specification does not reasonably provide enablement for the full scope of tubulin polymerization-inhibitory active substances having anti-tumor activity in combination the full scope of anti-inflammatory active substances. Applicants disagree with this assertion by the Examiner.

MPEP § 2164.01 states:

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.

This ground of rejection largely relates to the breadth of the genus of tubulin polymerization-inhibitory active substances having anti-tumor activity and the genus of anti-inflammatory active substances that are suitable for use in the present invention. However, Applicants submit that the full scope of these respective classes are extensively described in

the specification and the references cited therein so as to readily enable the skilled artisan to appreciate the full scope of the claimed invention without any experimentation.

For example, in regard to the tubulin polymerization-inhibitory active substances having anti-tumor activity Applicants direct the Examiner's attention to page 1, line 26 to page 2, line 6, which provides a series of references disclosing the same, stating:

Among the anti-tumor agents currently under development relates to medical agents (anti-tumor agents), which contain a tubulin polymerization-inhibitory active substance as an effective component. (Refer to Biochem. Mol. Biol. Int. 25 (6), 1153-1159 (1995); Br. J. Cancer 71 (4), 705-711 (1995); J. Med. Chem. 34 (8), 2579-2588 (1991); Biochemistry 28 (17), 6904-6991 (1989); US Patent No. 5,561,122; Japanese Laid-Open Patent Application JP-A-07-228,558(1995); Japanese Laid-Open Patent Application JP-A-08-301,831(1996); etc.).

Further, at page 5, line 12 to page 6, line 20, Applicants provide a detailed description of the class of tubulin polymerization-inhibitory active substances having anti-tumor activity, including many specific examples of compounds that may be used in the present invention and citing several additional references disclosing the same. These references, which represent the state of the art, include: J. Med. Chem. 41: 3022-3032 (1998); Bioorg. Med. Chem. Lett. 8:3153-3158 (1998); Bioorg. Med. Chem. Lett. 8:3371-3374 (1998); US Patent No. 5,430,062; WO 93/23,357, WO 99/51,246, WO 00/48,606.

Even further, Applicants painstakingly describe a genus of stilbene derivatives at page 13, line 12 to page 16, line 15, which may be used as tubulin polymerization-inhibitory active substances having anti-tumor activity. Also referred to in these pages to further represent the skilled artisan's appreciation of the genus of tubulin polymerization-inhibitory active substances having anti-tumor activity are the following representative references: US Patent Nos. 4,996,237; 5,561,122 and 5,430,062; and Japanese Laid-Open Patent Applications JP-A-07-228,558(1995); JP-A-08-301,831(1996) and JP-A-10-81,673(1998).

Turning to anti-inflammatory active substances, at page 6, lines 21 to page 7, line 12, Applicants provide an account of representative agents so as to engender in the mind of the skilled artisan the full scope of the same.

MPEP §2164.04 states:

“A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.”

In view of the foregoing, Applicants submit that determining what compounds fall within the scope of the two recited classes of compounds in Claim 1 would be readily apparent to the skilled artisan. Further, Applicants provide a detailed example at pages 22-26 utilizing a representative compound for each of the classes recited in Claim 1. Specifically, AC-7700 was selected as a representative tubulin polymerization-inhibitory active substances having anti-tumor activity, while dexamethasone was selected as a representative anti-inflammatory active substance. Since the skilled artisan is in possession of the knowledge of the full scope of the individual classes of compounds for the reasons above, selecting and evaluating various combinations for evaluation by the method detailed in the Examples of the present specification would require ordinary experimentation, surely not undue experimentation.

Based on the Examiner's rationale for this ground of rejection at page 5, lines 1-4 of the Office Action mailed May 20, 2005, it appears that the Examiner confuses quantity of experimentation with undue experimentation. However, quantity of experimentation is insufficient to support this ground of rejection. MPEP §2164.06 states:

... quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention. "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

Applicants submit that, with the present specification in hand, determination of the compounds within the scope of the present invention and their anti-tumor activity would require nothing more than routine experimentation, even though the protocols may appear to be complex or the amount of *routine* work may appear vast.

Therefore, Applicants have met their burden of clearly defining the scope of the claimed compounds, how to make the compounds, and how to use the compounds. Accordingly, this ground of rejection is unsustainable and should be withdrawn.

The rejection of Claims 1-4, 6-8, 10, and 12-15 under 35 U.S.C. §103(a) over Pettit or Cushman et al in view of Fex et al is respectfully traversed.

The Examiner cites Pettit and Cushman et al as disclosing tubulin polymerization-inhibitory active substances having anti-tumor activity. However, as the Examiner recognizes, these disclosures are silent with respect to the presence or co-administration of anti-inflammatory active substances.

In an attempt to remedy this deficiency in Pettit and Cushman et al, the Examiner cites Fex et al, which discloses an anti-inflammatory active substance. However, at no point does Fex et al disclose or suggest admixture of the anti-inflammatory active substance with a tubulin polymerization-inhibitory active substances having anti-tumor activity.

Accordingly, the Examiner relies on a general motivation to combine Pettit or Cushman et al with Fex et al since each of these disclosures relate to anti-tumor activity. In making this assertion the Examiner states “one skilled in the art would have assumed the combination of two individual anti-tumor active substances into a single composition would give an additive effect in the absence of evidence to the contrary.” However, this statement of the general assumption of an additive effect is exactly the reason why the combination is undesirable.

In cancer therapeutics, cytotoxicity is of grave concern. Cytotoxicity generally arises in many different ways, including dosage of an individual drug, total drug dosage, duration of treatment, drug-drug interaction, etc. Therefore, even though one drug or class of drugs may be safe and effective for treatment of tumors, it does not logically follow that the same effect would be observed when this drug or class of drugs is combined with some other drug or class of drugs, even if this other drug or class of drugs is also individually safe and effective for treatment of tumors. In fact, as the Examiner asserts if it is expected that the drugs would operate in an additive manner, then there would follow an expectation that the drug toxicities would, minimally, be additive as well thus *reducing* the amount of the anti-tumor drug that may be safely administered.

On page 2, line to page 3, line 5 of the present specification, Applicants discuss this very problem and how the present invention seeks to overcome these obstacles. Specifically, at this point in the specification Applicants reveal how the present invention expands the utility of tubulin polymerization-inhibitory active substances by maintaining the pharmaceutically effective dosage, increasing the lethal dosage, and improving the toxicity at the pharmaceutically effective dosage by admixture with an anti-inflammatory active substance.

Moreover, in the Examples of the present invention, Applicants use dexamethasone to demonstrate the effect of anti-inflammatory active substances on tubulin polymerization-inhibitory active substances as represented by AC-7700. In this Example, Applicants demonstrate that co-administration of an anti-inflammatory active substance with a tubulin polymerization-inhibitory active substance results in no significant difference between the anti-tumor effect of the tubulin polymerization-inhibitory active substance as compared to individual administration of the same (see page 25, lines 11-14).

More importantly, these results also show that co-administration of these drugs results in an *increase* in the maximum tolerable dose of the tubulin polymerization-inhibitory active substance by more than 2-fold (see page 25, line 18 to page 26, line 2). As stated above, the Examiner's statement of the general expectation in the outstanding Office Action that the effects of co-administration are additive would mean that there would likely be a decrease in the maximum tolerable dose of the active substance, not the observed 2-fold increase.

In view of the foregoing, Applicants submit that the present invention is not obvious in view of the disclosures of Pettit or Cushman et al in view of Fex et al. Applicants request withdrawal of this ground of rejection.

Applicants submit that the present application is now in condition for allowance.

Early notice to this effect is earnestly solicited.

Respectfully submitted,

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